EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201402164

Efficient Domino Synthesis of Pyrrole-Fused Isocoumarins with Microwave Heating

Mu-Yan Sun,[a][‡] Xiao-Yan Meng,[a][‡] Fu-Jie Zhao,[a][‡] Yi-Jing Dang,[a][‡] Fei Jiang,[a][‡] Kai Liu,[a][‡] Cong-Shuai Wang,[a][‡] Bo Jiang,*[a] and Shu-Jiang Tu*[a]

Keywords: Synthetic methods / Domino reactions / Oxygen heterocycles / Nitrogen heterocycles / Regioselectivity / Microwave chemistry

A new three-component approach to polyfunctionalized isochromeno[4,3-*b*]pyrroles has been developed with excellent regioselectivity. During these domino reactions, two ring-opening and three cyclization reactions were readily achieved through carbon–carbon bond cleavage under transition-metal-free conditions. The advantages of atom and step economy, and scope make this reaction a powerful tool for assembling tri-heterocyclic scaffolds of general chemical and biomedical interest.

Introduction

The development of highly efficient syntheses of multiheterocyclic scaffolds, particularly of those containing isocoumarin rings, is of chemical and biomedical importance and has been actively pursued in organic and medicinal research for several decades.[1,2] The structurally diverse and intriguing isocoumarin family has been found to exist in many natural products, for example cytogenin, bergenin, fusarentin, monocerin and cephalosol (Figure 1), and exhibit significant biological activities, such as antiallergenic, antimicrobial,[1,2] immunomodulatory,[3] cytotoxic,[4] antifungal,[5] antiinflammatory,[6] antiangiogenic,[7] and antimalarial.[8] There are a few methods to synthesize isocoumarin derivatives by using transition-metal complexes, such as Rh,[9] Pd,[10] Ru[11] and Cu[12] as the catalysts. Despite these limited isocoumarin syntheses, the development of a facile protocol for the direct formation of fused isocoumarin derivatives would be highly favorable.

In addition, multicomponent reactions (MCRs) have emerged as effective methods for the assembly of complex cyclic structures through the combination of two or more distinct reactions into a one-pot transformation.[13] MCRs can enhance annulation efficiency and also avoid time-consuming isolation of intermediates and minimize the generation of waste. In recent years, enormous efforts have been made to conduct multicomponent domino reactions toward the formation of various heterocycles.[14] However, to the best of our knowledge, the use of multicomponent reactions combined with insertion for the construction of a tricyclic pyrrole-fused isocoumarin skeleton through carbon–carbon bond cleavage has not been documented.

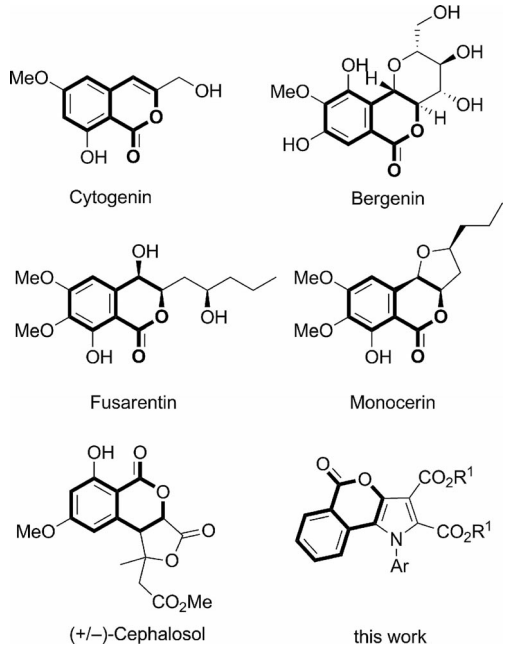
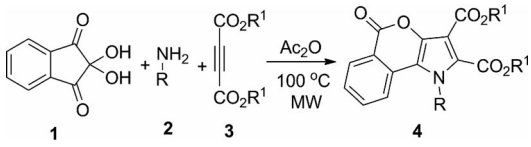


Figure 1. Some naturally occurring bioactive isocoumarins.

Recently, we have established several multicomponent domino reactions for a series of heterocycles.[15] In continuation of this project, we now report the challenging ring expansion and annulation of 2,2-dihydroxyindene-1,3-dione (**1**) with aromatic amines **2** and symmetrical dimethyl but-

[a] School of Chemistry and Chemical Engineering, and Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Jiangsu Normal University,
Xuzhou 211116, P. R. China
E-mail: jiangchem@jsnu.edu.cn
laotu@jsnu.edu.cn
[‡] These authors contributed equally to this work
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402164.

2-ynedioates **3** to yield multifunctionalized pyrrole-fused isocoumarin derivatives (Scheme 1). The advantage of the present multicomponent domino reactions is the formation of two new rings (pyran-2-one and pyrrole rings) and four sigma bonds that were readily achieved through a metal-free ring-expansion reaction in a one-pot operation; and the cyclopentenedione ring was converted into the corresponding pyran-2-one unit by insertion of oxygen into the sp^2–sp^3 C–C bond of the 2,2-dihydroxyindene-1,3-dione ring under transition-metal-free conditions. The present work represents a special example for construction of tricyclic heterocycles containing and isocoumarin unit with high regioselectivity.



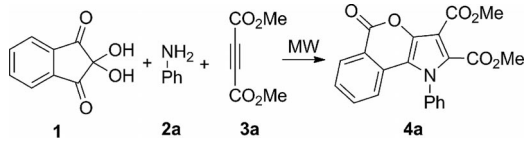
Scheme 1. The synthesis of polysubstituted fused isocoumarins **4**.

Results and Discussion

2,2-Dihydroxyindene-1,3-dione, which possesses three electrophilic centers, has proven to be an important building block for the construction of important cyclic skeletons.[16] Our strategy for the synthesis of highly functionalized tricyclic isocoumarins started from the reaction of 2,2-dihydroxyindene-1,3-dione with aromatic amines **2** and dimethyl but-2-ynedioate **3**, based on the fact that: (1) dimethyl but-2-ynedioate would undergo nucleophilic addition with amines, generating a β-enamino ester with 1,3-bisnucleophilic centers;[17] (2) 2,2-dihydroxyindene-1,3-dione was subjected to appropriate 1,3-bisnucleophiles to give dihydroxyindenes, which were converted into isocoumarin derivatives in acidic media.[18]

Based on the above analysis, the reaction of 2,2-dihydroxyindene-1,3-dione **1** with aniline **2a** and dimethyl but-2-ynedioate **3a** was tested under a variety of conditions. Representative data are summarized in Table 1. The reaction did not give desired product **4** in acidic solvents, such as formic acid (HCOOH) and CF_3COOH, at 80 °C under microwave irradiation (Table 1, Entries 1 and 2). An incomplete reaction was observed when acetic acid was used as the acidic media (Table 1, Entry 3). Gratifyingly, this reaction worked more efficiently in acetic anhydride, which afforded corresponding product **4a** in 59% yield (Table 1, Entry 4). Next, the influence of reaction temperature was also optimized, and the same reaction in Ac_2O was performed and repeated many times at different temperatures in a sealed vessel under microwave irradiation for 24 min. The yield of product **4a** was increased from 59 to 73% as the temperature increased from 80 to 100 °C, respectively (Table 1, Entry 5). Further increase in the reaction temperature failed to improve the yield of desired product **4a** (Table 1, Entry 6). Subsequently, the identical reaction was investigated under conventional heating at 100 °C for 60 min to provide desired product **4a** in 65% yield (Table 1, Entry 7).

Table 1. Optimization of reaction conditions.

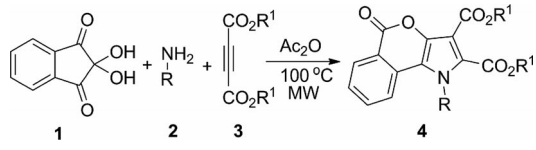


Entry	Solvent	*T* [°C]	Time [min]	Yield [%]
1	CF_3COOH	80	24	–
2	HCOOH	80	24	–
3	HOAc	80	24	21
4	Ac_2O	80	24	59
5	Ac_2O	100	24	73
6	Ac_2O	120	24	61
7	Ac_2O	100[a]	60[a]	65

[a] Conventional heating.

With acceptable conditions in hand, we proceeded to probe the substrate diversity of the three-component domino reaction by using readily available starting materials. Pleasingly, all the reactions proceeded efficiently and afforded the desired products in good to excellent yields. The results are presented in Table 2. The substituents on the arylamine ring did not hamper the reaction. Reactions of fluoro-, chloro-, bromo-, methyl-, or methoxy-substituted arylamine ring **2** with **1** and **3** all worked well to provide

Table 2. The domino synthesis of compounds **4**.[a]

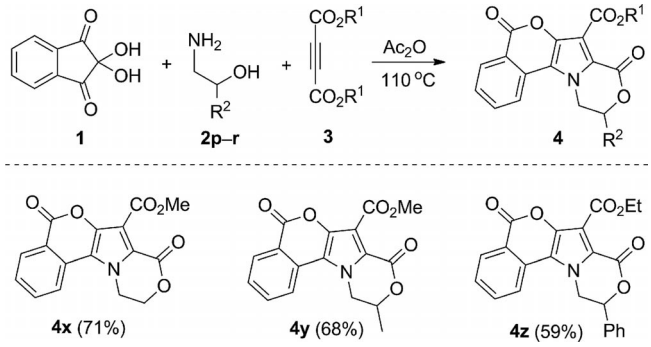


Entry	4	R (**2**)	R	Time[b]	Yield [%][c]
1	**4a**	Ph (**2a**)	Me (**3a**)	24	73
2	**4b**	3,5-F_2Ph (**2b**)	Me (**3a**)	21	68
3	**4c**	3-FPh (**2c**)	Me (**3a**)	25	76
4	**4d**	4-ClPh (**2d**)	Me (**3a**)	25	72
5	**4e**	3,4-Cl_2Ph (**2e**)	Me (**3a**)	26	75
6	**4f**	3,5-Cl_2Ph (**2f**)	Me (**3a**)	22	74
7	**4g**	4-BrPh (**2g**)	Me (**3a**)	24	77
8	**4h**	3-BrPh (**2h**)	Me (**3a**)	23	78
9	**4i**	4-MePh (**2i**)	Me (**3a**)	21	88
10	**4j**	3-Br-4-MePh (**2j**)	Me (**3a**)	26	86
11	**4k**	2-MePh (**2k**)	Me (**3a**)	23	71
12	**4l**	3-MePh (**2l**)	Me (**3a**)	24	75
13	**4m**	4-MeOPh (**2m**)	Me (**3a**)	21	79
14	**4n**	Me (**2n**)	Me (**3a**)	30	53
15	**4o**	Cyclopropyl (**2o**)	Me (**3a**)	28	64
16	**4p**	Ph (**2a**)	Et (**3b**)	21	81
17	**4q**	3,5-F_2Ph (**2b**)	Et (**3b**)	25	66
18	**4r**	4-ClPh (**2d**)	Et (**3b**)	28	77
19	**4s**	3,4-Cl_2Ph (**2a**)	Et (**3b**)	25	79
20	**4t**	3,5-Cl_2Ph (**2f**)	Et (**3b**)	23	72
21	**4u**	3-Br-4-MePh (**2j**)	Et (**3b**)	22	82
22	**4v**	4-MePh (**2i**)	Et (**3b**)	25	85
23	**4w**	Cyclopropyl (**2o**)	Et (**3b**)	28	60

[a] Reagents and conditions: 100 °C, Ac_2O (1.5 mL), microwave heating. [b] Time [min]. [c] Isolated yield.

the desired products in good yields (Table 2, Entries 1–13). Bulky *o*-substituted arylamine **2k** was converted into corresponding isochromeno[4,3-*b*]pyrroles **4k** in 71% yield. Similarly, methylamine **2n** and cyclopropanamine **2o** still displayed high reactivity and a clean reaction under these conditions (Table 2, Entries 14 and 15). Furthermore, diethyl but-2-ynedioate **3b** was suitable for this transformation. Next, amino alcohols were employed to replace aromatic amines to test the scope of this three-component domino reaction. As anticipated, 2-aminoethanol (**2p**), 1-aminopropan-2-ol (**2q**), and 2-amino-1-phenylethanol (**2r**) were all transformed into corresponding tetracyclic isocoumarin derivatives **4x**–**4z** in 59–71% yields (Scheme 2). These results display the scope and generality of the three-component cyclization reaction with regard to a wide range of amine components, including amino alcohols, aromatic, aliphatic, and alicyclic amines. The tolerance of functionalities, such as chloro and bromo in this protocol provides the opportunity for further chemical manipulations of the products. It is worth mentioning that the protocol provides a straightforward pathway to synthesize poly-substituted isochromeno[4,3-*b*]pyrroles, which are generally prepared through multi-step reactions.[19]

In all cases the reaction was very fast and complete within 21–30 min. Water is nearly the sole by-product, which makes work-up convenient. In most cases, the products precipitate when a dilute basic solution is poured into the reaction mixture. The structural elucidation was



Scheme 2. Domino synthesis of tetracyclic isocoumarins.

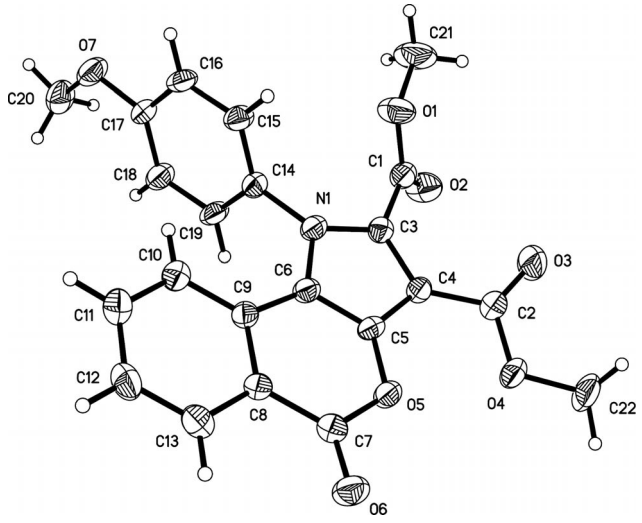
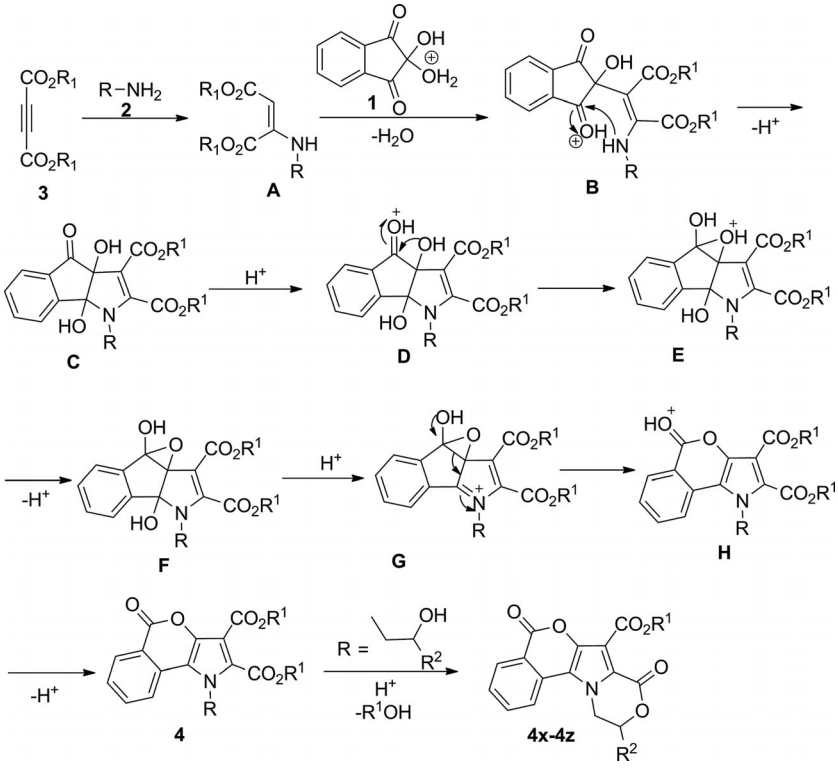


Figure 2. The ORTEP drawing of **4m**.[20]



Scheme 3. Proposed mechanism for formation of products **4**.

unequivocally determined by NMR spectroscopic analysis and single-crystal X-ray diffraction of **4m** (Figure 2).

On the basis of literature reports[18c] and observations from the above results, a possible mechanism for this new reaction is proposed and is depicted in Scheme 3. Firstly, an addition reaction between dimethyl but-2-ynedioate **3** and arylamines **1** occurs to generate β-enamino ester **A**, which reacts with protonated **2** providing intermediate **B**. Intermediate **B** undergoes intramolecular two continuous cyclizations to give three-membered ring-intermediate **G**, followed by ring-opening and deprotonation to yield isochromeno[4,3-*b*]pyrroles **4**. Isochromeno[4,3-*b*]pyrroles **4x**–**4z** are obtained through a third cyclization (intramolecular esterification).

Conclusions

In summary, we have described a new three-component domino reaction involving a ring-opening and cyclization process, which provides a general and efficient strategy for the synthesis of isochromeno[4,3-*b*]pyrrole derivatives with good yields in a one-pot manner. The bond-forming efficiency, structural accessibility and reaction generality make the present method a highly attractive approach to pyrrole-fused isocoumarin scaffolds of chemical and biomedical importance. Advantages of this strategy include the relatively mild conditions, convenient one-pot operation, and short reaction times. Efforts toward the extension of this methodology to natural products and drug synthesis are underway.

Experimental Section

General: Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage, Uppsala, Sweden. The reaction temperatures were measured with an infrared detector during microwave heating.

General Procedure for the Synthesis of Compounds 4a–4w

Dimethyl 5-Oxo-1-phenyl-1,5-dihydroisochromeno[4,3-*b*]pyrrole-2,3-dicarboxylate (4a): Microwave Heating: Dimethyl but-2-ynedioate (**3a**; 1.0 mmol, 0.142 g) was introduced into a 10-mL Initiator reaction vial, and aniline (**2a**; 1.0 mmol, 0.093 g) was slowly added. The mixture was stirred at room temperature for 6 min. Subsequently, 2,2-dihydroxyindene-1,3-dione (**1**; 1.0 mmol, 0.178 g) and Ac_2O (1.5 mL) were added. The reaction vial was capped and stirred for 20 s. The mixture was irradiated (time: 24 min, temperature: 100 °C; absorption level: high; fixed hold time) until TLC (petroleum ether/acetone, 3:1) revealed that conversion of starting material **1** was complete. The reaction mixture was cooled to room temperature. The diluted basic solution was poured into the reaction mixture until Ac_2O was neutralized, and then cold water (30 mL) was added. The solid product was filtered and washed with water and EtOH (95%), and subsequently dried and recrystallized from EtOH (95%) to give pure product **4a**.

Conventional Heating: Dimethyl but-2-ynedioate (**3a**; 1.0 mmol, 0.142 g) was introduced into a 10-mL Initiator reaction vial, and aniline (**2a**; 1.0 mmol, 0.093 g) was slowly added. The mixture was stirred at room temperature for 6 min. Subsequently, 2,2-dihydroxyindene-1,3-dione (**1**; 1.0 mmol, 0.178 g) and Ac_2O (1.5 mL) were added. The reaction vial was capped and stirred in an oil bath at 100 °C for 60 min. The work-up was as described for the above reaction to give a white solid; m.p. 265–266 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.26–8.24 (m, 1 H, Ar-H), 7.73–7.69 (m, 1 H, Ar-H), 7.68–7.64 (m, 2 H, Ar-H), 7.61–7.55 (m, 3 H, Ar-H), 7.52–7.48 (m, 1 H, Ar-H), 6.39 (d, J = 7.6 Hz, 1 H, Ar-H), 3.87 (s, 3 H, OCH_3), 3.63 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 162.1, 161.1, 160.5, 138.7, 137.0, 135.6, 131.8, 131.0, 130.4, 129.6, 129.5 (6), 128.6, 128.2, 119.7, 119.3, 116.0, 105.9, 53.2, 52.6 ppm. IR (KBr): $\tilde{\nu}$ = 3062, 1728, 1720, 1614, 1584, 1556, 1513, 1439, 1407 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{16}NO_6$ 378.0978 [M + H]$^+$; found 378.0999.

Dimethyl 1-(3,5-Difluorophenyl)-5-oxo-1,5-dihydroisochromeno-[4,3-*b*]pyrrole-2,3-dicarboxylate (4b): A white solid; m.p. > 300 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.29–8.27 (m, 1 H, Ar-H), 7.73–7.67 (m, 2 H, Ar-H), 7.61–7.54 (m, 3 H, Ar-H), 6.56 (d, J = 8.0 Hz, 1 H, Ar-H), 3.88 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.7, 161.1 (J_{CF}^1 = 216.5 Hz), 160.8, 139.5, 138.6, 136.0, 131.9, 129.2, 128.8, 128.7 (J_{CF}^3 = 8.2 Hz), 126.8 (J_{CF}^4 = 4.4 Hz), 120.0, 119.4, 116.6, 113.5 (J_{CF}^2 = 28.0 Hz), 107.7, 107.2, 53.2, 52.9 ppm. IR (KBr): $\tilde{\nu}$ = 3084, 1737, 1720, 1616, 1585, 1557, 1512, 1479 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{14}F_2NO_6$ 414.0789 [M + H]$^+$; found 414.0799.

Dimethyl 1-(3-Fluorophenyl)-5-oxo-1,5-dihydroisochromeno[4,3-*b*]-pyrrole-2,3-dicarboxylate (4c): A white solid; m.p. 177–178 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.26 (d, J = 8.0 Hz, 1 H, Ar-H), 7.74–7.58 (m, 4 H, Ar-H), 7.55–7.48 (m, 2 H, Ar-H), 6.45 (d, J = 8.0 Hz, 1 H, Ar-H), 3.86 (d, J = 11.2 Hz, 3 H, OCH_3), 3.68 (d, J = 10.4 Hz, 3 H, OCH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3049, 1734, 1721, 1610, 1556, 1496, 1455, 1408 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{15}FNO_6$ 396.0883 [M + H]$^+$; found 396.0877.

Dimethyl 1-(4-Chlorophenyl)-5-oxo-1,5-dihydroisochromeno[4,3-*b*]-pyrrole-2,3-dicarboxylate (4d): A white solid; m.p. 224–225 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.27–8.25 (m, 1 H, Ar-H), 7.75–7.71 (m, 2 H, Ar-H), 7.67–7.63 (m, 3 H, Ar-H), 7.55–7.51 (m, 1 H, Ar-H), 6.50 (d, J = 8.0 Hz, 1 H, Ar-H), 3.87 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 162.1, 161.0, 160.35, 138.7, 136.1, 135.8, 135.6, 131.9, 130.6, 130.5, 129.4, 128.4, 127.9, 119.8, 119.4, 116.3, 106.7, 53.2, 52.7 ppm. IR (KBr): $\tilde{\nu}$ = 3072, 1727, 1710, 1612, 1556, 1517, 1494, 1461 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{15}ClNO_6$ 412.0588 [M + H]$^+$; found 412.0594.

Dimethyl 1-(3,4-Dichlorophenyl)-5-oxo-1,5-dihydroisochromeno-[4,3-*b*]pyrrole-2,3-dicarboxylate (4e): A white solid; m.p. 231–232 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.27 (d, J = 7.6 Hz, 1 H, Ar-H), 8.10–8.09 (m, 1 H, Ar-H), 7.94 (d, J = 8.8 Hz, 1 H, Ar-H), 7.71–7.67 (m, 2 H, Ar-H), 7.55 (t, J = 7.6 Hz, 1 H, Ar-H), 6.57 (d, J = 8.0 Hz, 1 H, Ar-H), 3.88 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 162.2, 160.9, 160.1, 138.6, 137.1, 136.0, 133.9, 132.6, 132.2, 131.9, 131.0, 129.3, 129.2 (7), 128.6, 126.9, 120.0, 119.4, 116.7, 107.6, 53.2, 52.9 ppm. IR (KBr): $\tilde{\nu}$ = 3064, 1727, 1720, 1614, 1585, 1557, 1509, 1474, 1409 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{14}Cl_2NO_6$ 446.0198 [M + H]$^+$; found 446.0188.

Dimethyl 1-(3,5-Dichlorophenyl)-5-oxo-1,5-dihydroisochromeno-[4,3-*b*]pyrrole-2,3-dicarboxylate (4f): A white solid; m.p. 249–250 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.29–8.27 (m, 1 H, Ar-H), 8.03 (t, J = 2.0 Hz, 1 H, Ar-H), 7.91 (d, J = 1.6 Hz, 2 H, Ar-H), 7.73–7.69 (m, 1 H, Ar-H), 7.59–7.55 (m, 1 H, Ar-H), 6.53 (d, J = 8.0 Hz, 1 H, Ar-H), 3.89 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 162.2, 160.8, 160.0, 139.5, 138.6, 136.1, 135.3, 132.0, 131.0, 129.2, 128.7, 128.2, 126.4, 120.0, 119.4, 116.9, 108.0, 53.2, 52.9 ppm. IR (KBr): $\tilde{\nu}$ =

3066, 1731, 1722, 1612, 1573, 1555, 1508, 1439 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{14}Cl_2NO_6$ 446.0198 $[M + H]^+$; found 446.0185.

Dimethyl 1-(4-Bromophenyl)-5-oxo-1,5-dihydroisochromeno[4,3-*b*]-pyrrole-2,3-dicarboxylate (4 g): A white solid; m.p. 230–231 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.27–8.25 (m, 1 H, Ar-H), 7.89–7.85 (m, 2 H, Ar-H), 7.68–7.64 (m, 1 H, Ar-H), 7.61–7.57 (m, 2 H, Ar-H), 7.55–7.51 (m, 1 H, Ar-H), 6.50 (d, J = 8.0 Hz, 1 H, Ar-H), 3.87 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 162.1, 161.0, 160.4, 138.7, 136.5, 135.8, 133.4, 131.9, 130.8, 129.4, 128.4, 127.9, 124.2, 119.8, 119.4, 116.3, 106.7, 53.2, 52.7 ppm. IR (KBr): $\tilde{\nu}$ = 3070, 1733, 1724, 1611, 1556, 1518, 1493, 1460 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{15}BrNO_6$ 456.0083 $[M + H]^+$; found 456.0087.

Dimethyl 1-(3-Bromophenyl)-5-oxo-1,5-dihydroisochromeno[4,3-*b*]-pyrrole-2,3-dicarboxylate (4h): A white solid; m.p. 236–237 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.27–8.25 (m, 1 H, Ar-H), 7.96–7.91 (m, 2 H, Ar-H), 7.68–7.60 (m, 3 H, Ar-H), 7.55–7.51 (m, 1 H, Ar-H), 6.44 (d, J = 7.6 Hz, 1 H, Ar-H), 3.88 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 162.1, 160.9, 160.25, 138.6, 138.5 (7), 135.8, 134.0, 132.1, 131.9, 131.6, 129.4, 128.4, 128.0, 127.5, 122.5, 119.8, 119.4, 116.5, 107.0, 53.2, 52.8 ppm. IR (KBr): $\tilde{\nu}$ = 3060, 1732, 1720, 1614, 1557, 1509, 1476, 1439 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{15}BrNO_6$ 456.0083 $[M + H]^+$; found 456.0097.

Dimethyl 5-Oxo-1-(*p*-tolyl)-1,5-dihydroisochromeno[4,3-*b*]pyrrole-2,3-dicarboxylate (4i): A white solid; m.p. 190–191 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.25–8.23 (m, 1 H, Ar-H), 7.61–7.57 (m, 1 H, Ar-H), 7.52–7.48 (m, 1 H, Ar-H), 7.46 (s, 4 H, Ar-H), 6.46 (d, J = 8.0 Hz, 1 H, Ar-H), 3.86 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 2.48 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 162.0, 161.1, 160.6, 140.7, 138.7, 135.6, 134.4, 131.8, 130.8, 129.6, 129.0, 128.3, 128.2, 119.7, 119.2, 115.9, 105.6, 53.2, 52.6, 21.4 ppm. IR (KBr): $\tilde{\nu}$ = 3074, 1734, 1726, 1613, 1555, 1511, 1461, 1434 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{18}NO_6$ 392.1134 $[M + H]^+$; found 392.1166.

Dimethyl 1-(3-Bromo-4-methylphenyl)-5-oxo-1,5-dihydroisochromeno[4,3-*b*]pyrrole-2,3-dicarboxylate (4j): A white solid; m.p. 232–233 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.27–8.25 (m, 1 H, Ar-H), 7.92 (d, J = 2.0 Hz, 1 H, Ar-H), 7.67–7.62 (m, 2 H, Ar-H), 7.57–7.51 (m, 2 H, Ar-H), 6.51 (d, J = 8.0 Hz, 1 H, Ar-H), 3.87 (s, 3 H, OCH_3), 3.67 (s, 3 H, OCH_3), 2.50–2.49 (m, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 162.1, 161.0, 160.4, 140.6, 138.6, 135.9, 135.8, 132.4, 132.0, 131.9, 129.5, 128.4, 127.9 (4), 127.9 (1), 124.7, 119.8, 119.3, 116.4, 106.7, 53.2, 52.7, 22.8 ppm. IR (KBr): $\tilde{\nu}$ = 3080, 1733, 1724, 1614, 1557, 1509, 1491, 1438, 1407 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{17}BrNO_6$ 470.0239 $[M + H]^+$; found 470.0235.

Dimethyl 5-Oxo-1-(o-tolyl)-1,5-dihydroisochromeno[4,3-*b*]pyrrole-2,3-dicarboxylate (4k): A white solid; m.p. 224–225 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.27–8.24 (m, 1 H, Ar-H), 7.63–7.51 (m, 4 H, Ar-H), 7.49–7.47 (m, 2 H, Ar-H), 6.28 (d, J = 7.6 Hz, 1 H, Ar-H), 3.88 (s, 3 H, OCH_3), 3.63 (s, 3 H, OCH_3), 1.98 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 162.1, 161.1, 160.5, 138.8, 136.7, 136.3, 135.9, 131.9, 131.7, 131.3, 129.5, 128.7, 128.3, 128.1, 127.8, 119.4, 118.8, 115.4, 106.0, 53.2, 52.6, 17.1 ppm. IR (KBr): $\tilde{\nu}$ = 3060, 1723, 1710, 1611, 1552, 1504, 1439, 1402 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{18}NO_6$ 392.1134 $[M + H]^+$; found 392.1153.

Dimethyl 5-Oxo-1-(m-tolyl)-1,5-dihydroisochromeno[4,3-*b*]pyrrole-2,3-dicarboxylate (4l): A white solid; m.p. 224–225 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.26–8.24 (m, 1 H, Ar-H), 7.61–7.48 (m, 4 H, Ar-H), 7.40–7.37 (m, 2 H, Ar-H), 6.43 (d, J = 8.0 Hz, 1 H, Ar-H), 3.87 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 2.41 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 162.1, 161.1, 160.6, 140.2, 138.7, 136.9, 135.6, 131.8, 131.6, 130.1, 129.6, 128.8, 128.7, 128.2, 125.6, 119.8, 119.3, 115.9, 105.7, 53.2, 52.6, 21.2 ppm. IR (KBr): $\tilde{\nu}$ = 3074, 1729, 1711, 1613, 1583, 1556, 1511, 1489, 1402 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{18}NO_6$ 392.1134 $[M + H]^+$; found 392.1122.

Dimethyl 1-(4-Methoxyphenyl)-5-oxo-1,5-dihydroisochromeno-[4,3-*b*]pyrrole-2,3-dicarboxylate (4m): A white solid; m.p. 223–224 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.26–8.23 (m, 1 H, Ar-H), 7.64–7.60 (m, 1 H, Ar-H), 7.52–7.48 (m, 3 H, Ar-H), 7.19–7.15 (m, 2 H, Ar-H), 6.51 (d, J = 8.0 Hz, 1 H, Ar-H), 3.89 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 3.65 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 162.1, 161.1, 160.8, 160.7, 138.6, 135.7, 131.8, 129.8, 129.7, 129.3, 129.2, 128.1, 119.7, 119.2, 116.0, 115.4, 105.4, 56.1, 53.2, 52.6 ppm. IR (KBr): $\tilde{\nu}$ = 3075, 1745, 1719, 1613, 1584, 1556, 1513, 1459, 1441 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{18}NO_7$ 408.1083 $[M + H]^+$; found 408.1078.

Dimethyl 1-Methyl-5-oxo-1,5-dihydroisochromeno[4,3-*b*]pyrrole-2,3-dicarboxylate (4n): A white solid; m.p. 238–239 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.31 (d, J = 8.0 Hz, 1 H, Ar-H), 8.20 (d, J = 8.0 Hz, 1 H Ar-H), 7.96 (t, J = 7.6 Hz, 1 H, Ar-H), 7.64 (t, J = 7.6 Hz, 1 H, Ar-H), 4.16 (s, 3 H, CH_3), 3.90 (s, 3 H, CH_3), 3.83 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 162.2, 161.5, 161.2, 138.6, 136.0, 131.8, 130.0, 128.1, 127.6, 121.6, 119.1, 115.7, 104.9, 53.5, 52.5, 36.2 ppm. IR (KBr): $\tilde{\nu}$ = 3058, 1743, 1691, 1636, 1563, 1474 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{13}NO_6Na$ 338.0635 $[M + Na]^+$; found 338.0633.

Dimethyl1-cyclopropyl-5-oxo-1,5-dihydroisochromeno[4,3-*b*]pyrrole-2,3-dicarboxylate(4o): A white solid; m.p. 232–234 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.45 (d, J = 8.4 Hz, 1 H, Ar-H), 8.28 (d, J = 8.0 Hz, 1 H, Ar-H), 7.96 (t, J = 8.0 Hz, 1 H, Ar-H), 7.62 (t, J = 7.6 Hz, 1 H, Ar-H), 3.93 (s, 3 H, CH_3), 3.91–3.88 (m, 1 H, CH), 3.81 (s, 3 H, CH_3), 1.32–1.28 (m, 2 H, CH_2), 0.99–0.95 (m, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.8, 161.7, 161.3, 138.3, 135.7, 131.5, 130.8, 130.0, 127.9, 122.3, 118.9, 116.1, 103.6, 53.6, 52.3, 31.0, 10.3 ppm. IR (KBr): $\tilde{\nu}$ = 3068, 1733, 1690, 1633, 1559, 1478 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{15}NO_6Na$ 364.0792 $[M + Na]^+$; found 364.0798.

Diethyl 5-Oxo-1-phenyl-1,5-dihydroisochromeno[4,3-*b*]pyrrole-2,3-dicarboxylate (4p): A white solid; m.p. 127–128 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.26–8.23 (m, 1 H, Ar-H), 7.73–7.64 (m, 3 H, Ar-H), 7.61–7.55 (m, 3 H, Ar-H), 7.52–7.48 (m, 1 H, Ar-H), 6.40 (d, J = 8.0 Hz, 1 H, Ar-H), 4.35–4.30 (m, 2 H, CH_2), 4.09–4.04 (m, 2 H, CH_2), 1.30 (t, J = 7.2 Hz, 3 H, CH_3), 1.00 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.0, 160.5, 159.3, 138.2, 136.7, 135.0, 132.1, 131.3, 130.4, 129.8, 129.1, 128.1, 127.6, 119.1, 118.8, 115.3, 105.6, 61.4, 60.7, 14.0, 13.4 ppm. IR (KBr): $\tilde{\nu}$ = 3058, 1726, 1719, 1615, 1557, 1498, 1444, 1402 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{20}NO_6$, 406.1291 $[M + H]^+$; found 406.1289.

Diethyl 1-(3,5-Difluorophenyl)-5-oxo-1,5-dihydroisochromeno-[4,3-*b*]pyrrole-2,3-dicarboxylate (4q): A white solid; m.p. 220–221 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.29–8.27 (m, 1 H, Ar-H), 7.72–7.67 (m, 2 H, Ar-H), 7.64–7.54 (m, 3 H, Ar-H), 6.57 (d, J = 8.0 Hz, 1 H, Ar-H), 4.37–4.31 (m, 2 H, CH_2), 4.15–4.10 (m, 2 H, CH_2), 1.31 (t, J = 6.8 Hz, 3 H, CH_3), 1.08 (t, J = 7.2 Hz, 3 H, CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3070, 1737, 1708, 1616, 1557, 1509, 1474, 1402 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{18}F_2NO_6$ 442.1102 $[M + H]^+$; found 442.1084.

Diethyl 1-(4-Chlorophenyl)-5-oxo-1,5-dihydroisochromeno[4,3-*b*]pyrrole-2,3-dicarboxylate (4r): A white solid; m.p. 156–157 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.27–8.25 (m, 1 H, Ar-H), 7.76–7.72 (m, 2 H, Ar-H), 7.68–7.63 (m, 3 H, Ar-H), 7.55–7.51 (m, 1 H, Ar-H), 6.50 (d, J = 8.0 Hz, 1 H, Ar-H), 4.35–4.30 (m, 2 H, CH$_2$), 4.12–4.06 (m, 2 H, CH$_2$), 1.31 (t, J = 7.2 Hz, 3 H, CH$_3$), 1.05 (t, J = 6.8 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.6, 161.0, 159.7, 138.7, 136.3, 135.8, 135.5, 131.9, 130.7, 130.4, 129.5, 128.3, 127.8, 119.8, 119.4, 116.2, 107.1, 62.0, 61.4, 14.5, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3097, 1737, 1720, 1611, 1556, 1496, 1455, 1437, 1409 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{19}ClNO_6$ 440.0901 [M + H]$^+$; found 440.0919.

Diethyl 1-(3,4-Dichlorophenyl)-5-oxo-1,5-dihydroisochromeno-[4,3-*b*]pyrrole-2,3-dicarboxylate (4s): A white solid; m.p. 194–195 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.27 (d, J = 8.0 Hz, 1 H, Ar-H), 8.11–8.10 (m, 1 H, Ar-H), 7.94 (d, J = 8.8 Hz, 1 H, Ar-H), 7.71–7.68 (m, 2 H, Ar-H), 7.55 (t, J = 7.6 Hz, 1 H, Ar-H), 6.58 (d, J = 8.0 Hz, 1 H, Ar-H), 4.36–4.31 (m, 2 H, CH$_2$), 4.14–4.08 (m, 2 H, CH$_2$), 1.31 (t, J = 7.2 Hz, 3 H, CH$_3$), 1.06 (t, J = 7.2 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.7, 160.9, 159.5, 138.6, 137.3, 136.0, 133.9, 132.6, 132.1, 132.0, 131.1, 129.4, 129.3, 128.5, 126.8, 120.0, 119.4, 116.6, 108.0, 62.0, 61.6, 14.5, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3068, 1733, 1726, 1614, 1557, 1475, 1439, 1411 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{18}Cl_2NO_6$ 474.0511 [M + H]$^+$; found 474.0523.

Diethyl 1-(3,5-Dichlorophenyl)-5-oxo-1,5-dihydroisochromeno-[4,3-*b*]pyrrole-2,3-dicarboxylate (4t): A white solid; m.p. 188–189 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.29–8.27 (m, 1 H, Ar-H), 8.02 (t, J = 2.0 Hz, 1 H, Ar-H), 7.91 (d, J = 1.6 Hz, 2 H, Ar-H), 7.73–7.68 (m, 1 H, Ar-H), 7.58–7.54 (m, 1 H, Ar-H), 6.56 (d, J = 8.0 Hz, 1 H, Ar-H), 4.37–4.31 (m, 2 H, CH$_2$), 4.15–4.10 (m, 2 H, CH$_2$), 1.31 (t, J = 7.2 Hz, 3 H, CH$_3$), 1.07 (t, J = 7.2 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.7, 160.9, 159.3, 139.7, 138.6, 136.0, 135.2, 132.0, 130.9, 129.2, 128.6, 128.3, 126.4, 120.0, 119.4, 116.7, 108.4, 62.0, 61.6, 14.5, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3067, 1736, 1721, 1614, 1583, 1510, 1446, 1407 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{18}Cl_2NO_6$ 474.0511 [M + H]$^+$; found 474.0522.

Diethyl 1-(3-Bromo-4-methylphenyl)-5-oxo-1,5-dihydroisochromeno[4,3-*b*]pyrrole-2,3-dicarboxylate (4u): A white solid; m.p. 161–162 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.27–8.25 (m, 1 H, Ar-H), 7.93 (d, J = 2.0 Hz, 1 H, Ar-H), 7.67–7.62 (m, 2 H, Ar-H), 7.57–7.50 (m, 2 H, Ar-H), 6.53 (d, J = 8.0 Hz, 1 H, Ar-H), 4.35–4.30 (m, 2 H, CH$_2$), 4.13–4.07 (m, 2 H, CH$_2$), 1.30 (t, J = 7.2 Hz, 3 H, CH$_3$), 1.05 (t, J = 6.8 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.6, 161.0, 159.7, 140.5, 138.7, 136.1, 135.8, 132.3, 132.1, 131.9, 129.5, 128.3, 128.0, 127.8, 124.7, 119.8, 119.3, 116.2, 107.0, 62.0, 61.4, 22.8, 14.5, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3083, 1750, 1716, 1613, 1554, 1515, 1494, 1412 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{21}BrNO_6$ 498.0552 [M + H]$^+$; found 498.0552.

Diethyl 5-Oxo-1-(*p*-tolyl)-1,5-dihydroisochromeno[4,3-*b*]pyrrole-2,3-dicarboxylate (4v): A white solid; m.p. 160–161 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.26–8.24 (m, 1 H, Ar-H), 7.61–7.57 (m, 1 H, Ar-H), 7.52–7.50 (m, 1 H, Ar-H), 7.48–7.45 (m, 4 H, Ar-H), 6.48 (d, J = 8.0 Hz, 1 H, Ar-H), 4.34–4.29 (m, 2 H, CH$_2$), 4.10–4.05 (m, 2 H, CH$_2$), 2.47 (s, 3 H, CH$_3$), 1.30 (t, J = 7.2 Hz, 3 H, CH$_3$), 1.03 (t, J = 7.2 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.6, 161.1, 160.0, 140.7, 138.7, 135.6, 134.6, 131.8, 130.8, 129.7, 128.9, 128.4, 128.1, 119.7, 119.3, 115.7, 105.8, 62.0, 61.2, 21.4, 14.5, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3072, 1744, 1727, 1613, 1554, 1514, 1465, 1401 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{22}NO_6$ 420.1447 [M + H]$^+$; found 420.1454.

Diethyl 1-Cyclopropyl-5-oxo-1,5-dihydroisochromeno[4,3-*b*]pyrrole-2,3-dicarboxylate (5w): A white solid; m.p. 199–200 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.45 (d, J = 8.0 Hz, 1 H, Ar-H), 8.28 (d, J = 8.0 Hz, 1 H, Ar-H), 7.96 (t, J = 8.0 Hz, 1 H, Ar-H), 7.62 (t, J = 8.0 Hz, 1 H, Ar-H), 4.41–4.36 (m, 2 H, CH$_2$), 4.29–4.24 (m, 2 H, CH$_2$), 3.93–3.88 (m, 1 H, CH), 1.35 (t, J = 8.0 Hz, 3 H, CH$_3$), 1.31–1.26 (m, 5 H, CH$_3$ and CH$_2$), 1.00–0.96 (m, 2 H, CH$_2$) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.3, 161.2, 138.4, 135.7, 31.5, 130.9, 130.0, 127.9, 122.3, 118.9, 116.0, 103.8, 62.6, 60.9, 30.9, 14.6, 14.2, 10.5 ppm. IR (KBr): $\tilde{\nu}$ = 3065, 1721, 1695, 1630, 1559, 1473 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{19}NO_6Na$ 392.1105 [M + Na]$^+$; found 392.1106.

Methyl 5,8-Dioxo-5,8,10,11-tetrahydroisochromeno[3′,4′:4,5]-pyrrolo[2,1-*c*][1,4]oxazine-7-Carboxylate (4x): A gray solid; m.p. 299–300 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.25 (d, J = 8.0 Hz, 1 H, Ar-H), 7.90 (t, J = 8.0 Hz, 1 H, Ar-H), 7.81 (d, J = 8.0 Hz, 1 H, Ar-H), 7.57 (t, J = 8.0 Hz, 1 H, Ar-H), 4.70 (t, J = 5.2 Hz, 2 H, CH$_2$), 4.36 (t, J = 5.6 Hz, 2 H, CH$_2$), 3.93 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 165.4, 159.7, 157.3, 141.4, 136.6, 133.3, 131.7, 127.8, 122.7, 118.3, 115.9, 112.6, 99.7, 66.4,53.3 ppm. IR (KBr): $\tilde{\nu}$ = 3053, 1720, 1705, 1687, 1567, 1483 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{11}NO_6$ 313.0586 [M – H]$^-$; found 313.0595.

Methyl 10-Methyl-5,8-dioxo-5,8,10,11-tetrahydroisochromeno-[3′,4′:4,5]pyrrolo[2,1-*c*][1,4]oxazine-7-carboxylate (4y): A red solid; m.p. > 300 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.24 (d, J = 8.0 Hz, 1 H, Ar-H), 7.90 (t, J = 7.6 Hz, 1 H, Ar H), 7.81 (d, J = 8.0 Hz, 1 H, Ar-H), 7.57 (t, J = 7.6 Hz, 1 H, Ar-H), 7.97–7.92 (m, 1 H, CH$_2$), 4.58–4.40 (m, 1 H, CH$_2$), 4.04–4.00 (m, 1 H, CH), 3.94 (s, 3 H, CH$_3$), 1.46 (d, J = 6.4 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 165.4, 164.7, 159.7, 141.3, 136.6, 133.3, 131.7, 127.8, 122.7, 118.3, 115.7, 112.2, 99.8, 74.3, 53.3, 44.6, 17.9 ppm. IR (KBr): $\tilde{\nu}$ = 3058, 1753, 1674, 1628, 1550, 1467 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{13}NO_6Na$ 326.0635 [M + Na]$^+$; found 362.0645.

Ethyl 5,8-Dioxo-10-phenyl-5,8,10,11-tetrahydroisochromeno-[3′,4′:4,5]pyrrolo[2,1-*c*][1,4] oxazine-7-carboxylate (4z): A white solid; m.p. 262–263 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.32 (d, J = 8.0 Hz, 1 H, Ar-H), 7.19 (d, J = 8.0 Hz, 1 H, Ar-H),7.92 (t, J = 8.0 Hz, 1 H, Ar-H), 7.70–7.61 (m, 3 H, Ar-H), 7.51 (t, J = 4.0 Hz, 3 H, Ar-H),6.09–6.05 (m, 1 H, CH), 5.17–5.13 (m, 1 H, CH), 4.84 (t, J = 12.0 Hz, 1 H, CH), 4.50 (s, 2 H, CH$_2$), 4.38–4.31 (m, 2 H, CH$_2$),1.33 (t, J = 8.0 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.5, 160.8, 156.6, 135.6, 131.8, 129.8, 129.1, 127.9, 127.6, 122.6, 119.8, 118.6, 115.6, 108.6, 97.2, 78.2, 61.5, 54.9, 48.3, 31.2, 14.5 ppm. IR (KBr): $\tilde{\nu}$ = 3065, 1738, 1646, 1632, 1551, 1478 cm^{-1}. HRMS (ESI): calcd. For $C_{23}H_{17}NO_6$ 403.1056 [M – H]$^-$; found 403.1066.

General Procedure for the Synthesis of Compounds 4x–4z

Methyl 5,8-Dioxo-5,8,10,11-tetrahydroisochromeno[3′,4′:4,5]-pyrrolo[2,1-*c*][1,4]oxazine-7-carboxylate (4x): Dimethyl but-2-ynedioate (**3a**; 1.0 mmol, 0.142 g) was introduced into a 10-mL Initiator reaction vial, and 2-aminoethanol (**2p**; 1.0 mmol, 0.061 g) was slowly added at 0 °C. The mixture was stirred at room temperature for 8 min. Subsequently, 2,2-dihydroxyindene-1,3-dione (**1**; 1.0 mmol, 0.178 g) and Ac_2O (1.5 mL) were added. The reaction vial was capped and stirred for 20 s. The mixture was irradiated (time: 25 min, temperature: 110 °C; absorption level: high; fixed hold time) until TLC (petroleum ether/acetone, 3:1) revealed that

conversion of starting material **1** was complete. The reaction mixture was cooled to room temperature. The diluted basic solution was poured into the reaction mixture until Ac_2O was neutralized, and then cold water (30 mL) was added. The solid product was filtered and washed with water and EtOH (80%), and subsequently dried and recrystallized from EtOH (80%) to give pure product **4x** as a gray solid; m.p. 299–300 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.25 (d, J = 8.0 Hz, 1 H, Ar-H), 7.90 (t, J = 8.0 Hz, 1 H, Ar-H), 7.81 (d, J = 8.0 Hz, 1 H, Ar-H), 7.57 (t, J = 8.0 Hz, 1 H, Ar-H), 4.70 (t, J = 5.2 Hz, 2 H, CH_2), 4.36 (t, J = 5.6 Hz, 2 H, CH_2), 3.93 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 165.4, 159.7, 157.3, 141.4, 136.6, 133.3, 131.7, 127.8, 122.7, 118.3, 115.9, 112.6, 99.7, 66.4, 53.3 ppm. IR (KBr): $\tilde{\nu}$ = 3053, 1720, 1705, 1687, 1567, 1483 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{11}NO_6$ 313.0586 [M – H]$^-$; found 313.0595.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra of products **4a**–**4x**.

Acknowledgments

The authors are grateful for financial support from the National Natural Science Foundation of China (NSFC) (grant numbers 21272095 and 21102124), Jiangsu Science and Technology Support Program (grant number SBE2011045), the Qing Lan Project (grant number 12QLG006), and National Students' Innovative Training Program (grant number 201310320020Z). Mr Wei Fan is thanked for his generous assistance.

[1] H. Matsuda, H. Shimoda, M. Yoshikawa, *Bioorg. Med. Chem.* **1999**, *7*, 1445.
[2] a) M. Yoshikawa, E. Harada, Y. Naitoh, K. Inoue, H. Matsuda, H. Shimoda, J. Yamahara, N. Murakami, *Chem. Pharm. Bull.* **1994**, *42*, 2225; b) M. Weigele, R. Czajkowski, J. F. Blount, S. De Bernardo, J. P. Tengi, W. Leimgruber, *J. Org. Chem.* **1976**, *41*, 390; c) M. Weigele, J. F. Blount, J. P. Tengi, R. C. Czajkowski, W. Leimgruber, *J. Am. Chem. Soc.* **1972**, *94*, 4052.
[3] H. Matsuda, H. Shimoda, J. Yamahara, M. Yoshikawa, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 215.
[4] A. C. Whyte, J. B. Gloer, J. A. Scoot, D. Mallock, *J. Nat. Prod.* **1996**, *59*, 765.
[5] K. Nozawa, M. Yamada, Y. Tsuda, K. Kawai, S. Nakajima, *Chem. Pharm. Bull.* **1981**, *29*, 2689.
[6] T. Furuta, Y. Fukuyama, Y. Asakawa, *Phytochemistry* **1986**, *25*, 517.
[7] J. H. Lee, Y. J. Park, H. S. Kim, Y. S. Hong, K. W. Kim, *Antibiotics* **2001**, *54*, 463.
[8] M. Chinworungsee, P. Kittakoop, M. Isaka, R. Chanphen, M. Tanticharoen, Y. J. Thebtaranonth, *J. Chem. Soc. Perkin Trans. 1* **2002**, *34*, 2473.
[9] a) M. Shimizu, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2009**, *74*, 3478; b) T. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2007**, *9*, 1407; c) K. Ueura, T. Satoh, M. Miura, *J. Org. Chem.* **2007**, *72*, 5362.
[10] a) P. Zhao, D. Chen, G. Song, K. Han, X. Li, *J. Org. Chem.* **2012**, *77*, 1579; b) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285; c) R. C. Larock, M. J. Doty, X. Han, *J. Org. Chem.* **1999**, *64*, 8770; d) R. C. Larock, E. K. Yum, M. J. Doty, K. K. C. Sham, *J. Org. Chem.* **1995**, *60*, 3270.
[11] a) R. K. Chinnagolla, M. Jeganmohan, *Chem. Commun.* **2012**, *48*, 2030; b) L. Ackermann, J. Pospech, K. Graczyk, K. Rauch, *Org. Lett.* **2012**, *14*, 930.
[12] a) X.-X. Guo, *J. Org. Chem.* **2013**, *78*, 1660; b) V. Kavala, C.-C. Wang, D. K. Barange, C.-W. Kuo, P.-M. Lei, C.-F. Yao, *J. Org. Chem.* **2012**, *77*, 5022.
[13] a) R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating, *Acc. Chem. Res.* **1996**, *29*, 123; b) A. DomLing, *Chem. Rev.* **2006**, *106*, 17; c) *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienayme), Wiley-VCH, Weinheim, Germany, **2005**; d) L. F. Tietze, T. Kinzel, C. C. Brazel, *Acc. Chem. Res.* **2009**, *42*, 367.
[14] a) B. Jiang, T. Rajale, W. Walter, S.-J. Tu, G. Li, *Chem. Asian J.* **2010**, *5*, 2318; b) E. Ruijter, R. Scheffelaar, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2011**, *50*, 6234; *Angew. Chem.* **2011**, *123*, 6358; c) V. Estevez, M. Villacampa, J. C. Menendez, *Chem. Soc. Rev.* **2010**, *39*, 4402; d) B. Ganem, *Acc. Chem. Res.* **2009**, *42*, 463; e) G. Li, H. X. Wei, S. H. Kim, M. D. Carducci, *Angew. Chem. Int. Ed.* **2001**, *40*, 4277; *Angew. Chem.* **2001**, *113*, 4407.
[15] a) W. Fan, Q. Ye, H.-W. Xu, B. Jiang, S.-L. Wang, S.-J. Tu, *Org. Lett.* **2013**, *15*, 2258; b) B. Jiang, X. Wang, H.-W. Xu, M.-S. Tu, S.-J. Tu, G. Li, *Org. Lett.* **2013**, *15*, 1540; c) B. Jiang, B.-M. Feng, S.-L. Wang, S.-J. Tu, G. Li, *Chem. Eur. J.* **2012**, *18*, 9823; d) T.-J. Li, H.-M. Yin, C.-S. Yao, X.-S. Wang, B. Jiang, S.-J. Tu, G. Li, *Chem. Commun.* **2012**, *48*, 11966.
[16] a) A. Alizadeh, A. Rezvanian, L.-G. Zhu, *J. Org. Chem.* **2012**, *77*, 4385; b) J. L. Bullington, J. H. Dodd, *J. Org. Chem.* **1993**, *58*, 4833; c) S. Das, R. Frohlich, A. Pramanik, *Org. Lett.* **2006**, *8*, 4263; d) C. Cheng, B. Jiang, S.-J. Tu, G. Li, *Green Chem.* **2011**, *13*, 2107; e) B. Jiang, Q.-Y. Li, S.-J. Tu, G. Li, *Org. Lett.* **2012**, *14*, 5210.
[17] Y. Han, Y. Sun, J. Sun, C.-G. Yan, *Tetrahedron* **2012**, *68*, 8256.
[18] a) S. Pathak, A. Kundu, A. Pramanik, *Tetrahedron Lett.* **2011**, *52*, 5180; b) I. Yavari, S. Seyfi, M. Nematpour, Z. Hossaini, *Helv. Chim. Acta* **2010**, *93*, 1413; c) J. L. Bullington, J. H. Dodd, *J. Org. Chem.* **1993**, *58*, 4833.
[19] F. Bihel, G. Quéléver, H. Lelouard, A. Petit, C. Alvès da Costa, O. Pourquié, F. Checler, A. Thellend, P. Pierree, J.-L. Krausa, *Bioorg. Med. Chem.* **2003**, *11*, 3141.
[20] CCDC-962595 (for **4m**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif: $C_{22}H_{17}NO_7$, crystal dimension 0.28 × 0.15 × 0.12 mm, monoclinic, space group $P2_1/c$, a = 8.4172(7) Å, b = 13.5815(15) Å, c = 16.8652(17) Å, α = 90.00°, β = 92.6520(10)°, γ = 90.00°, V = 1925.9(3) Å^3, Mr = 407.37, Z = 4, Dc = 1.405 Mg/m^3, λ = 0.71073 Å, μ(Mo-K_α) = 0.106 mm^{-1}, F(000) = 848, R = 0.0489, wR_2 = 0.0831, S = 1.051, largest diff. peak and hole: 0.0184 and –0.187 e/Å^3.

Received: February 27, 2014
Published Online: ■

Domino Reactions

A new three-component approach to polyfunctionalized isochromeno[4,3-*b*]pyrroles has been developed with excellent regioselectivity.

Keywords: Synthetic methods / Domino reactions / Oxygen heterocycles / Nitrogen heterocycles / Regioselectivity / Microwave chemistry

